

Hepatitis A and B Infections



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KEYWORDS

• Hepatitis A • Hepatitis B • Virus

KEY POINTS

- Hepatitis A causes acute viral hepatitis. The symptoms of nausea, vomiting, fatigue, and jaundice are self-limited.
- Hepatitis A infections are infrequent in the United States because of routine vaccination of children.
- Hepatitis B infrequently causes symptomatic acute viral hepatitis. When it does, it also presents with nausea, vomiting, abdominal pain, and jaundice.
- Hepatitis B can progress into chronic viral hepatitis, which increases the risk of developing cirrhosis and hepatocellular carcinoma.
- The incidence of hepatitis B infections is declining in the United States because of routine vaccination of children; however, significant morbidity and mortality from chronic hepatitis B still exist.

HISTORY

Epidemic jaundice has plagued the human race for centuries, with the first description found in writings by Hippocrates from the fifth century BC. Historically, epidemic jaundice was likely a combination of hepatitis A and B, because they could not be differentiated until the advent of modern medicine. Mass immunization against both hepatitis A and B began in the United States in the late twentieth century, which has drastically reduced the incidence of both hepatitis A and B.¹

HEPATITIS A

Epidemiology

Hepatitis A virus (HAV) infections in the United States are very rare. The HAV vaccine became available in 1995, and since that time, incidence has decreased by 95%.² In 2014, there were only 1239 reported cases of HAV in the United States.² Accounting for underreporting and missed cases, the Centers for Disease Control and Prevention (CDC) estimates that there were likely nearly 2500 cases.

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Virus Description

HAV is a small, nonenveloped, RNA virus of the genus *Hepatovirus*. The virus was first isolated in 1979, and humans are its only natural host. HAV is a hardy virus; it can tolerate a pH as low as 1 as well as high heat.³ HAV can also survive on surfaces outside of the human body for months.³ This leads to easy transmission and explains the historic jaundice epidemics. It is also why both proper hygiene and decreasing the number of available hosts and reservoirs through vaccination are key factors to decreasing the incidence of HAV infection.

Transmission and Life Cycle

HAV undergoes fecal-oral transmission. Spread of the virus is increased by poor general hygiene, including absent or improper hand-washing after using the bathroom or changing diapers, before and during food preparation, and inadequate cleaning of bathroom and food preparation surfaces. The virus can be killed during proper cooking, but if food is not cooked thoroughly, or is contaminated after it is cooked, the virus can still be transmitted. In order to kill the virus, food must be heated to at least 185°F for 1 minute.^{3–5} Once inside the body, it can survive in the stomach because of its tolerance of low pH. Virions reach the liver through the portal circulation and replicate inside hepatocytes. The virus is then released into the bile ducts and enters the enterohepatic cycle until it is neutralized by antibodies.⁴

Risk Factors

HAV vaccine is a part of the standard childhood vaccination series recommended for all children in the United States. Since its mass implementation in 1995, the incidence of HAV transmission has drastically decreased, greatly lowering the overall risk for HAV in the United States. However, there are still many unvaccinated adults, and several situations increase the risk of contracting HAV. These situations include living in or traveling to areas with poor sanitation, household contact with persons with HAV, sexual contact with persons with HAV, and men who have sex with men.^{2,6} Any unvaccinated person with these high-risk behaviors should be vaccinated and educated on other risk reduction strategies.²

Incubation Period

The time from exposure to onset of symptoms ranges from 15 to 50 days, with an average of 28 days.^{3,4} Viral shedding in the stool can occur during the incubation period, as early as 2 weeks before the onset of symptoms.⁴ This time period is a time of increased risk of transmission because the patient does not yet know they are ill, and hand hygiene may be lax. The patient continues to shed the virus throughout the symptomatic period, and most viral shedding in the stool ends when clinical symptoms resolve. Interestingly, viral shedding in infants can continue for up to 5 months after clinical illness has resolved.³ Infants require caregiver support in hygiene and diaper changing, making this a significant potential source of transmission.

Clinical Illness

After a variable but highly contagious incubation period, patients enter the clinical stage of the disease. Symptoms of HAV infection are nonspecific and variable and can include fatigue, fever, nausea, vomiting, anorexia, abdominal pain, and jaundice.^{2–4} Illness severity ranges from asymptomatic to fulminant liver failure. Asymptomatic HAV is seen more commonly in infants and young children. Adults are more likely to experience symptoms, including jaundice. More than 70% of adult cases

demonstrate jaundice during the clinical phase.^{3,4} Nevertheless, fulminant liver failure is rare; symptoms are self-limited, and symptomatic treatment is the standard of care.

Evaluation

Given that the clinical presentation of HAV is nonspecific and the rate of HAV infection has decreased so dramatically, HAV infection should not be diagnosed on clinical features alone. Clinical suspicion is raised by an unvaccinated patient with recent exposure to HAV or participation in high-risk behaviors presenting with symptoms of fever, jaundice, nausea, vomiting, and joint pain. Evaluation of these patients should include liver functions tests, including serum total and unconjugated bilirubin, alkaline phosphatase, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), prothrombin time/international normalized ratio, and albumin. Typical laboratory abnormalities include elevations in AST and ALT, total and direct bilirubin, and alkaline phosphatase levels. ALT is usually higher than AST, and elevations can be notable, usually ranging from 500 to 5000 IU/L. These laboratory abnormalities suggest the diagnosis of acute hepatitis; however, the diagnosis of HAV relies on positive serologic testing for HAV immunoglobulin M (IgM) antibodies, or proving a strong epidemiologic link to a laboratory-confirmed case of hepatitis A.² IgM anti-HAV becomes positive after 5 days of illness, but does not remain positive for long after the acute infection has resolved. It can also become positive shortly after receiving the HAV vaccine. Seventy-five percent of acute hepatitis cases are caused by either hepatitis A or hepatitis B, and appropriate laboratory evaluation should be undertaken in patients presenting with symptoms of acute viral hepatitis.⁴

Treatment

Treatment of HAV is very straightforward. Treatment is limited to supportive care as needed for nausea, vomiting, and other symptoms, as well as education to prevent further transmission, stressing proper hand hygiene. Patients should not return to school or work until fever and jaundice have resolved.^{2,7}

Prevention

Prevention of HAV in the United States is largely accomplished through vaccination of all children at 1 year of age as well as adults deemed to be at high risk for HAV exposure which includes men who have sex with men, persons traveling to countries with high rates of hepatitis A, persons with risk for occupational exposure, persons with chronic liver disease, and household contacts of children recently adopted from hepatitis A endemic countries.² The HAV vaccine has greatly decreased the disease burden of hepatitis A in the United States. It is thought that the vaccine confers immunity for 25 years in adults and up to 20 years in children. There is no recommendation for booster doses at this time. Proper hand and surface hygiene at all times is also important prevention, especially during times of outbreak.^{2,6}

Screening

Because hepatitis A does not develop into a chronic state, no screening is indicated. All persons desiring immunity can be vaccinated. There is no indication to check for natural immunity. If patients are unsure of vaccination history and desire immunity, they can be vaccinated, because there is no known serious harm from receiving a second vaccination.²

HEPATITIS B***Epidemiology***

Routine vaccination of US children against the hepatitis B virus (HBV) began in 1991. In the last 20 years, HBV infection incidence in the United States has decreased 82%. However, unlike hepatitis A, acute HBV is more likely to be asymptomatic and can develop into a chronic infection. Even though the number of documented acute cases of HBV infection is similar to HAV, the estimated actual cases, clinical burden, and mortality from HBV are much higher. For example, in 2014, there were 2953 reported cases of acute HBV. However, acute HBV is only symptomatic 50% of the time; therefore, true acute cases are likely underreported, and it is estimated that there were approximately 19,200 acute cases in 2014.⁸

Chronic hepatitis B (CHB) is a more widespread problem and is estimated to affect between 850,000 and 2 million people in the United States alone. There were an estimated 53,800 new cases of CHB reported annually from 2004 to 2008, of which 95% were in immigrants from countries where hepatitis B is endemic.⁹ CHB infection has large implications for long-term health.

Virus Description

HBV is a double-stranded, enveloped, DNA virus of the Hepadnaviridae family. It is the smallest DNA virus known, with the DNA in a partly double-stranded, circular pattern.¹ It replicates in hepatocytes and causes dysfunction of the liver.¹

Transmission and Risk Factors

HBV is transmitted via the percutaneous or permucosal route. It is transmitted when the blood, semen, or vaginal fluids of an infected individual enter an uninfected person's body. Transmission can occur during sexual intercourse, through sharing of needles, when blood from an affected individual enters another person via an open wound or mucosal surface, and vertically from mother to child during childbirth. It is not spread through casual contact, but can be spread through close personal contact, especially if there are any cuts, wounds, or loss of normal skin barriers between both parties.¹

Incubation

The incubation period for HBV is variable, ranging from 45 to 180 days, which can make it difficult to determine where and when transmission occurred.¹ The hepatitis B surface antigen (HBsAg) can be detected in blood as early as 30 to 60 days after exposure.¹

Clinical Illness

Acute

HBV infection can cause an acute viral hepatitis with clinical manifestations similar to HAV infection. However, acute HBV infection is asymptomatic in up to 50% of patients.⁸ Jaundice is infrequent in young children, appearing in less than 10% of acute cases. It is more common in adults and older children, appearing during acute infection about 50% of the time. Symptoms are similar to those of HAV and include fever, malaise, abdominal pain, nausea, vomiting, and flu-like symptoms.^{1,8}

The laboratory workup for suspected acute HBV is identical to HAV and will show similar alterations in liver transaminases. During acute illness, there is a marked elevation of ALT and AST, at times greater than 1000. Bilirubin can be normal, especially if the patient is not jaundiced. Liver transaminases should return to normal within 4 months following acute infection. As in HAV infection, once acute hepatitis is identified, testing for HAV and HBV antibodies should be performed, because clinically, the

2 infections look very similar. An acute HBV infection will show a positive HBsAg and positive IgM HBV core antibodies (IgM anti-HBc), as further described in later discussion.^{1,10,11}

Treatment of acute HBV is similar to HAV treatment and consists of supportive care. Very few cases will develop into fulminant hepatic failure. Patients greater than the age of 60 are more likely to develop severe disease. The CDC reports that the fatality rate for acute HBV infection is 0.5% to 1%.⁸

Hepatitis B Virus Laboratory Values

An HBV panel of tests can be overwhelming; however the laboratory values are very informative and help delineate active versus previous infection, and acute versus chronic infection.

Hepatitis B surface antibody

The simplest antibody to understand is the hepatitis B surface antibody (anti-HBs). The anti-HBs is a protective antibody that will neutralize the virus.¹ When this value is positive, it indicates that the patient has immunity to HBV and is therefore no longer susceptible to acute infection nor chronically infected (**Table 1**). This value is checked when evaluating for past immunization or past infection. The anti-HBs is protective; therefore, there is no need to check other laboratory values, because the patient is neither acutely nor chronically infected and is protected from future infection. It cannot differentiate whether a person is immune through vaccination or from previous natural infection.

Hepatitis B core antibody

Hepatitis B core antibody (anti-HBc) indicates infection from the natural HBV. The HBV vaccination only contains HBsAg. It does not contain core components of the virus. Therefore, the anti-HBc is only positive in patients who have been exposed to naturally occurring HBV. It becomes positive following the incubation period, generally at the onset of symptoms, and remains positive for the life of the patient. Although this antibody indicates the patient has been exposed to HBV, it does not determine if the infection is acute, chronic, or cleared (**Table 2**). Only the presence of anti-HBs determines if the patient has cleared the infection. The concurrent presence of anti-HBc indicates the patient is immune from a natural infection, whereas its absence indicates the patient is immune from vaccination.¹

Hepatitis B surface antigen

The laboratory test most essential to understanding a patient's hepatitis B status is the HBsAg. If this value is positive, the patient is currently infected with HBV, either acutely or chronically (**Table 3**). It also indicates that the patient is infectious. If the HBsAg is negative, the patient is not currently infected. It does not distinguish past infection, only current infection. HBsAg remains positive for an average of 4 weeks, but will become negative by 15 weeks in all patients who have not developed chronic infection.⁸ Because the HBsAg is a marker of current infection, and it is known that a patient will have a positive anti-HBc value if their body has been exposed to the HBV, then it is

Table 1 Interpretation of hepatitis B virus surface antibody result					
	Susceptible to Infection	Immune, from Vaccination	Immune, past Infection	Chronic Infection	Acute Infection
Anti-HBs	Negative	Positive	Positive	Negative	Negative

Table 2 Interpretation of hepatitis B virus core antibody result					
	Susceptible to Infection	Immune from Vaccination	Immune, past Infection	Chronic Infection	Acute Infection
Anti-HBc	Negative	Negative	Positive	Positive	Positive

known that a positive HBsAg will always be accompanied by a positive anti-HBc. Also, because the HBsAg is a marker of current infection, it is known that the anti-HBs value will be negative, because the anti-HBs is a protective antibody and a marker of immunity.

Hepatitis B core antibody IgM

After a positive HBsAg, the next step is to determine if the patient has an acute or chronic HBV infection. The IgM antibody to HBV core components (IgM anti-HBc) remains positive for about 6 months after infection with HBV. If this value is positive, it indicates that the patient is acutely infected with HBV via a temporal association; if negative, the patient is chronically infected, because they have a positive HBsAg and the absence of the IgM anti-HBc means they must have been infected for more than 6 months (Table 4). Table 5 demonstrates how to interpret all results together.

Chronic

Although acute HBV is similar in clinical symptoms to acute HAV, the true risk and morbidity of HBV comes from its transformation into a chronic infection. The risk of progression to chronic HBV is largely dependent on the age at which the patient acquires the acute infection. The risk of progression to chronic is highest if the infection is acquired perinatally, with 90% of perinatal HBV infections becoming chronic.^{1,10} Children between the ages of 1 and 5 at the time of infection have a 25% to 50% risk of chronic infection. After age 6 years, there is a 10% risk of progression to chronic infection.¹

Chronic HBV infection is defined as having a positive HBsAg for more than 6 months, because all patients that will naturally clear the virus will do so within 15 weeks following infection.⁸ Once the patient has developed chronic HBV infection, they are at a significantly increased risk of developing chronic liver disease, including cirrhosis and hepatocellular carcinoma. Twenty-five percent of patients who develop CHB during childhood, and 15% of those who develop CHB later in life, will die prematurely from hepatocellular carcinoma or cirrhosis.⁸ In the United States alone, this accounts for approximately 1800 deaths per year.⁸

After identification of a CHB infection, patients require further evaluation of liver function, monitoring for cirrhosis, and consideration for possible treatment.¹² Persistent replication of the HBV leading to inflammation, cirrhosis, and hepatocellular carcinoma is the major factor in the morbidity and mortality of CHB. The goals of therapy are to reduce viral replication and damage to the liver. CHB has 5 phases, each with different

Table 3 Interpretation of hepatitis B virus surface antigen result					
	Susceptible to Infection	Immune from Vaccination	Immune from past Infection	Chronically Infected	Acutely Infected
HBsAg	Negative	Negative	Negative	Positive	Positive

Table 4
Interpretation of hepatitis B virus chronic immunoglobulin M antibody result

	Susceptible to Infection	Immune from Vaccination	Immune from past Infection	Chronically Infected	Acutely Infected
IgM anti-HBc				Negative	Positive

implications for treatment. The hepatitis B e antigen (HBeAg) is a marker of high levels of viral replication, and patients will start to develop anti-HBe as they are clearing the virus. Liver cirrhosis is linked to the immune response to HBV, and elevated ALT levels correlate with a high immune response, not necessarily a high viral load.⁹

Phases of Chronic Hepatitis B

There are 5 phases of chronic HBV infection, all of which have different implications for treatment and management.¹² Patients will not necessarily progress through every stage in order during their chronic infection.

Phases

1. Immune tolerant phase: In this phase, patients will have high levels of HBV replication but no identifiable immune response. The HBeAg is positive, because this is a marker of high viral replication. The inflammation and damage to the liver are thought to be related to the immune response, so during this phase, there is little to no fibrosis or inflammation of the liver (Table 6).¹²
2. Immune clearance phase (HBeAg-positive CHB): Patients will have high levels of HBV DNA and are HBeAg positive, similar to the immune tolerant phase, but because of high immune activity, there is elevation of the ALT and fibrosis and inflammation of the liver.
3. Low viral replication phase: During this phase, patients have developed anti-HBe and are no longer HBeAg positive; there are low levels of HBV replication and limited inflammation. Patients will still have a positive HBsAg and have not cleared the virus yet.
4. Reactivation phase (HBeAg-negative CHB): Following the loss of HBeAg and the development of anti-HBe, patients may go into this stage and develop fibrosis and inflammation. This stage is characterized by fluctuating levels of ALT.
5. Resolution: During this stage, patients will have cleared the virus and will become HBsAg negative.

Treatment options

Treatment is usually started when ALT levels are elevated, so the 2 most common phases that are treated are the immune clearance phase (HBeAg-positive CHB) and

Table 5
Interpretation of the hepatitis B panel of tests

	Susceptible to Infection	Immune from Vaccination	Immune from past Infection	Chronically Infected	Acutely Infected
Anti- HBs	–	+	+	–	–
Anti-HBc	–	–	+	+	+
HBsAg	–	–	–	+	+
IgM anti-HBc	–	–	–	–	+

+, positive; –,negative.

Table 6 Laboratory results and the phases of chronic hepatitis B					
Phase	HBsAg	HBeAg	HBV DNA	Anti-Hbe	ALT
Immune tolerant	+ >6 mo	+	↑↑	–	Normal or slightly elevated
Immune clearance phase (HBe-Ag-positive CHB)	+ >6 mo	+	↑↑	–	↑↑
Low viral replication	+ >6 mo	–	↓	+	Normal
Reactivation phase (HBeAg-negative CHB)	+ >6 mo	–	↑	+	↑↑
Resolution	–	–	Undetectable	+	Normal

↑↑, markedly elevated; ↑, mildly elevated; ↓, low.

the reactivation phase (HBeAg-negative CHB).⁹ There are currently 7 medications indicated for treatment of CHB. There are 5 oral nucleotide reverse transcriptase inhibitors as well as pegylated interferon alfa-2a and interferon.

The preferred first-line agents at this time are entecavir, tenofovir, and pegylated interferon alfa-2a. The most common treatments at this time are 1 year of pegylated interferon alfa-2a or prolonged treatment with an oral nucleotide reverse transcriptase inhibitor.⁹

Screening

The US Preventive Services Task Force (USPSTF) recommends that all pregnant women in the United States be screened for HBV during their initial obstetrical laboratory work.¹³ This screening allows physicians to identify women who are chronically infected with HBV and treat the infant at birth to prevent vertical transmission. All infants born to women who are infected with HBV are given hepatitis B immune globulin within 12 hours of birth and HBV vaccination at birth followed by appropriately timed second and third doses. This vaccination schedule decreases the risk of acute HBV infection in the infant to 4% to 10%, decreased from 90%.^{9,14} Women who have high levels of HBV DNA during pregnancy have an increased risk of transmission to the fetus. Therefore, it is reasonable to start treatment in pregnant woman in the final trimester of pregnancy. Telbivudine and tenofovir are category B and can be considered for treatment.⁹ Universal screening of all adults is not recommended, although it is a B recommendation by the USPSTF to screen adults who are at high risk for HBV exposure.¹³

Prevention

Immunization is recommended for all children beginning at birth in the United States. There are multiple other indications for vaccination, including all children less than 19 years who have not been vaccinated, men who have sex with men, and health care workers. There are multiple vaccination options, and all have different dosing schedules. Evidence suggests that the protection conferred by the vaccination lasts at least 20 years. There is no recommendation for a booster in immunocompetent individuals.⁸

Patients on hemodialysis should be screened yearly with an anti-HBs titer, as there are indications for booster vaccinations in hemodialysis patients. There is a recommendation to revaccinate hemodialysis patients when their titer of anti-HBs decreases

to less than 10 mIU/mL. For other immunocompromised patients, there is a similar recommendation for yearly screening of anti-HBs titer and a consideration of a booster vaccination if their titers decrease to less than 10 mIU/mL.⁸

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